

ROBUST SUMMARY OF TOXCITY OF METHANOL

INTRODUCTION

Methanol, a colorless, water-soluble simple alcohol containing one carbon atom, occurs naturally in plants and animals. Methanol has been used in industry for 100 years. It is a feedstock for chemical syntheses (for formaldehyde, acetic acid, and methyl tertiary-butyl ether and a solvent in a variety of consumer products (ie paints and varnishes, antifreeze, windshield washers, cleansing solutions, and adhesives) (World Health Organization 1997). Methanol is also a component or byproduct in various commercial operations such as sewage treatment, fermentation, and the pulp and paper industry.

In humans, methanol is derived both from the diet and from metabolic processes (Kavet and Nauss 1990, World Health Organization 1997). People ingest low doses of methanol in fruits, vegetables, and fermented beverages as well as soft drinks and foods sweetened with aspartame (which breaks down to methanol in the gastrointestinal tract)

There is abundant data on the potential health effects of methanol in humans. Most information on the human health effects of methanol is derived from clinical observations following accidental or intentional ingestion events. Methanol can be highly toxic resulting in nausea, dizziness, metabolic acidosis, and toxicity to the visual system (including blindness), motor disturbances and even death in humans. The absorption of methanol is rapid following oral ingestion, inhalation of methanol vapor, or skin contact. High doses of methanol overwhelm the body's ability to remove a toxic metabolite (formate). When formate accumulates, toxicity occurs

Animal tests were done over the years to obtain predictive information on health effects. Investigation of methanol toxicity in animals is somewhat difficult to correlate with human response because normal rodents (the most common laboratory test animal) exposed to methanol do not display the metabolic acidosis and toxicity to the visual system that occurs in humans (Roe 1982, Tephly and McMartin 1984; World Health Organization 1997).

Methanol is metabolized through the same pathways in humans and animals, but the differences in the rate of removal of metabolites result in the differences in methanol-induced toxicity. The data presented in this robust summary (IUCLID format) of key studies with some supplementary remarks and an added discussion about species differences supports the completeness of information needed for this HPV chemical.

This robust summary is prepared using the HPV subset of the IUCLID program format. The HPV subset calls for certain, not all, chapters of the IUCLID program. The chapters (profile) called for in the HPV program are listed on the next page. The use of the HPV subsets means the numbering of chapters is not always sequential. For some sections the IUCLID program uses drop down menus, while free text is used in other sections. The sections with drop down menu force a choice based on the drop down menu list. This can be confusing. For example, for question like what species was used might result in the choice of "other" (specific species not listed on drop down menu). In these cases we have indicate the specific species information in the method section which is a free text section.

I U C L I D

D a t a S e t

Existing Chemical	ID: 67-56-1
CAS No.	67-56-1
EINECS Name	methanol
EINECS No.	200-659-6
TSCA Name	Methanol
Molecular Formula	CH4O

Producer Related Part	
Company:	Bio Risk
Creation date:	22-FEB-2001

Substance Related Part	
Company:	Bio Risk
Creation date:	22-FEB-2001

Memo:	AMI
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Printing date:	23-MAR-2001
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Number of Pages:	65
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Chapter (profile):	Chapter: 2.1, 2.2, 2.4, 2.5, 2.6.1, 3.1.1, 3.1.2, 3.3.1, 3.5, 4.1, 4.2, 4.3, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.4, 5.5, 5.6, 5.8, 5.9
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Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
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Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS Date: 23-MAR-2001
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2.1 Melting Point

Value: = -97.8 degree C
Decomposition: no
Sublimation: no
Method: other
Year: 1983
GLP: no data
Test substance: no data
Reliability: (2) valid with restriction
16-MAR-2001
(84)

2.2 Boiling Point

Value: = 64.6 degree C
Method: other
Year: 1990
GLP: no data
Test substance: no data
Reliability: (4) not assignable
16-MAR-2001
(96)

Value: = 64.7 degree C at 760 hPa
Decomposition: no
Method: other
Year: 1983
GLP: no data
Test substance: no data
Remark: no data
Reliability: (2) valid with restrictions
14-MAR-2001
(84)

2.4 Vapour Pressure

Value: = 127 hPa at 25 degree C
Decomposition: no
Method: other (measured)
Year: 1984
GLP: no data
Test substance: no data
Reliability: (2) valid with restriction
08-MAR-2001
(15)

2.5 Partition Coefficient

log Pow: = -.77
Method: other (calculated)
Year: 1996
GLP: no data
Test substance: no data
Remark: See Sanger J., Octanol-water partition of simple organic compounds (1989) J. Phys. Chem. Ref. Data, Vol 18 No.3 p1150. Sanger reports a range of Log P from -0.32 to 0.83.
Reliability: (2) valid with restrictions
08-MAR-2001
(36)

2.6.1 Water Solubility

Qualitative: miscible
pKa: 15 at 25 degree C
pH: = 7
Method: other
Year: 1985
GLP: no data
Test substance: no data
Reliability: (2) valid with restrictions
22-MAR-2001
(34)

3. Environmental Fate and Pathways

ID: 67-56-1

3.1.1 Photodegradation

Type: air
 DIRECT PHOTOLYSIS
 Degradation: = 50 % after 17.8 day
 INDIRECT PHOTOLYSIS
 Sensitizer: OH
 Conc. of sens.: 500000 molecule/cm3
 Method: other (calculated)
 Year: 1990 GLP: no data
 Test substance: no data
 Remark: rate constant= 0.9×10^{-12} cm3/molecule sec
 Reliability: (2) valid with restrictions
 16-MAR-2001
 (7)

Type: air
 Method: other (measured)
 Year: 1989 GLP: no data
 Test substance: no data
 Remark: rate constant= $0.88 (+/-) \times 10^{-12}$ cm3/molecule*sec bei
 Reliability: (2) valid with restrictions
 16-MAR-2001
 (6)

Type: water
 INDIRECT PHOTOLYSIS
 Sensitizer: OH
 Method: other (calculated)
 Year: 1991 GLP: no data
 Test substance: no data
 Deg. Products
 Remark: $k(\text{OH}) = 8.46 \times 10^{-9}$ liter/mole OH concentration 5×10^{-14} mol/liter, temperature 298K
 Reliability: (2) valid with restrictions
 16-MAR-2001
 (46)

3.1.1 Photodegradation (Added Remarks)

Remark: Degradation of methanol by photolysis is not expected to be significant
 Reliability: (2) valid with restrictions
 21-MAR-2001
 (31)

Remark: Methanol in aqueous solution exhibited no degradation when

exposed to sunlight using an EPA test protocol. Sediment and clay suspension solutions did not photocatalyze the degradation of methanol in aqueous solution during irradiation with uv light

Reliability: (2) valid with restrictions
21-MAR-2001
(37)

3.1.2 Stability in Water

Type:
Method: other
Year: 1982 GLP: no data
Test substance: no data
Remark: Alcohols generally do not hydrolyze in water
Reliability: (2) valid with restrictions
16-MAR-2001
(52)

Type:
Method:
Year: GLP:
Test substance:
Remark: Abiotic degradation (i.e., non-biological or chemical) reactions are not likely to contribute significantly to methanol removal from surface water bodies. Hydrolysis reactions usually transform compounds into more polar products; methanol is a very polar molecule and is stable in water. Methanol has a measured Henry's Law Constant of 4.4×10^{-6} atm-cu m/mole at 250C. This value of Henry's Law constant indicates that volatilization from environmental waters may be significant. The volatilization half-life from a river (1 meter deep flowing 1 M/sec with a wind speed of 3 m/sec) has been 4.8 days. Degradation (i.e., non-biological or chemical) reactions are not likely to contribute significantly to methanol removal from surface water bodies. Hydrolysis reactions usually transform compounds into more polar products; methanol is a very polar molecule and is stable in water. Methanol has a measured Henry's Law Constant of 4.4×10^{-6} atm-cu m/mole at 250C. This value of Henry's Law Constant indicates that volatilization from environmental waters may be significant. The volatilization half-life from a river (1 meter deep flowing 1 M/sec with a wind speed of 3 m/sec) has been 4.8 days.
Reliability: (2) valid with restrictions
22-MAR-2001
(61)

3.3.1 Transport between Environmental Compartments

Type: volatility
Media: water - air
Air (Level I):
Water (Level I):
Soil (Level I):
Biota (L.II/III):
Soil (L.II/III):

Method: other
Year: 1982
Remark: Methanol has a measured Henry's Law constant of 4.4×10^{-6} atm*m³/mol at 25 deg C. Volatilization to environment maybe significant.
Reliability: (2) valid with restrictions
16-MAR-2001
(51)

Type: volatility
Media: water - air
Air (Level I):
Water (Level I):
Soil (Level I):
Biota (L.II/III):
Soil (L.II/III):
Method: other
Year: 1990
Remark: Howard estimated a half-life of 2.6 days for volatilization Of methanol from a pound. Using Henry's law constant and equation from Lyman (1982) half-life can be calculated for different conditions (wind, water flow rate and depth of water)..
Reliability: (2) valid with restrictions
16-MAR-2001
(40)

3.3.1 Transport between Environmental Compartments (Added Remarks)

Remark: The soil/water partition coefficient, Kd, can be used to estimate the rate of movement of a chemical in groundwater compared to the rate of groundwater flow. For non-ionic organic compounds such as methanol, Kd values are a function of the organic carbon content of the soil (foc) and the organic carbon based partition coefficient (Koc [L/kg]). In a soil/water environment, methanol will be present primarily in the water phase. The dissolved methanol will migrate at the velocity of groundwater except in soils with organic carbon fraction greater than 10 percent (i.e., for foc = 0.1 the Kd is approximately 0.8 signifying nearly equivalent concentrations of methanol adsorbed on soil and dissolved in water)
Reliability: (2) valid with restrictions
21-MAR-2001
(61)

Remark: Methanol is miscible and should have high mobility in soil and migrate with any surface water owing to low Ko/w value of -0.77. Based on a vapor pressure of 92mm Hg at 20 deg C evaporation form dry surfaces can be expected.
Reliability: (2) valid with restrictions
21-MAR-2001
(37)

3.5 Biodegradation

Type: aerobic
 Inoculum: activated sludge, adapted
 Degradation: = 50 - 80 % after 6 day
 Result: readily biodegradable
 Method: other
 Year: 1978 GLP: no data
 Test substance: no data
 Result: Adaptation of the sludge to 0.1% (v/v) methanol occurs over a period of several days. More than 80% of the methanol is then metabolized.
 Reliability: (2) valid with restrictions
 16-MAR-2001
 (83)

Type: aerobic
 Inoculum: activated sludge, adapted
 1.5 g/l related to COD (Chemical Oxygen Demand)
 Contact time: 29 day
 Degradation: = 95 % after 20 day
 Result: readily biodegradable
 5 day = 76 %
 10 day = 88 %
 15 day = 91 %
 20 day = 95 %
 Deg. Product: not measured
 Method: other
 Year: 1974 GLP: no data
 Test substance: no data
 Remark: The biodegradation in seawater was 69% *5 days), 84% (10 days). 85% (15 days), and 97% (20 days).
 Conclusion: Methanol is rapidly biodegraded in fresh and sea water.
 Reliability: (2) valid with restrictions
 16-MAR-2001
 (63)

Type: anaerobic
 Inoculum: predominantly domestic sewage
 Contact time: 182 hour(s)
 Degradation: >= 50 % after 7 hour(s)
 Result: readily biodegradable
 Deg. Product: yes
 Method: other
 Year: 1993 GLP: no data
 Test substance: no data
 Method: Sediment and groundwater were collected from a methaanogenic portion of a shallow anoxic aquifer polluted by municipal landfill leachate. Slurries were prepared by placing 50 g of sediment and 75 ml of groundwater in sterile 160-mL serum bottles. The bottles were sealed and incubated in the dark at room temperature. Each compound was added to the ncubation mixtures to reach an initial substrate concentration of 50 ppm. Pressure increases resulting from biogas formation (CH4 and C02) were monitored with an automated pressure transducer

system. At the end of the incubation period, the depletion of the parent substrate and the formation of methane over background controls were confirmed with a Varian 3300 gas chromatograph equipped with a flame ionization detector. The rate of substrate depletion was determined in incubations receiving a subsequent addition of the oxygenate. The amount of methane formed in aquifer incubations was compared to that theoretically expected based on the Buswell equation.

Conclusion: Methanol is rapidly biodegraded under anaerobic condition by sediment and groundwater polluted by municipal landfill leachate

Reliability: (2) valid with restrictions
16-MAR-2001
(82)

Type: anaerobic
Inoculum: other
Contact time: 4 month
Degradation: >= 98 % after 4 month
Result: readily biodegradable
Deg. Product: not measured
Method: other
Year: 1996 GLP: no data
Test substance: no data
Method: Microcosms were constructed in 0.5 or 1 liter capped glass bottles. The 1 liter bottles contained 200 grams of site soil and 0.9 liter of ground water. The 0.5 liter bottle had 150 grams of soil and 0,4 liter of water. Dissolved oxygen was measured. Hydrogen peroxide was added to some bottles as an oxygen source.

Result: Methanol is degraded under conditions of this study.
Reliability: (2) valid with restrictions
16-MAR-2001
(64)

3.5 Biodegradation (Added Remarks)

Remark: The biodegradation of methanol has been studied under a wide variety of conditions and media, including wastewater, surface water, sediments, groundwater, and in soil microcosms. Methanol is completely degraded and there are no persistent degradation intermediates.

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(38)

Remark: Biodegradation is the predominant removal process for Methanol in activated sludge treatment of pulp and paper Industry wastewater.

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(8)

Remark: Methanol added to natural microbial assemblages taken from a eutrophic lake in Georgia, from the Okefenokee Swamp and from mangrove stands degraded with half-lives between nine and 29

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(41)

days

Remark:
21-MAR-2001
(2)

Half-life can be long in dry soils (weeks to months).

Remark:

Removal during biological wastewater treatment is reported at 86-99 percent. Aqueous half-lives for aerobic and anaerobic biodegradation of methanol ranging from 24 to 168 hours (7 days). Methanol estimated half-life range from one to seven days in saturated soils.

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(39)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: flow through
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: c = 15400
Method: other
Year: 1986 GLP: no data
Test substance: other TS
Method: Analytical values determined by spectrofluorimeter. Water obtained from Lake Superior. Water chemistry evaluated along with dissolved oxygen. Five concentrations tested.
Result: Effects were noted almost immediately at two highest concentration. Most of the mortality was noted in 3 hours.
Test substance: Methanol (Burdick & Jackson)
Reliability: (1) valid without restrictions
09-MAR-2001
(62)

Type: flow through
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: c = 28100
Method: other
Year: 1983 GLP: no data
Test substance: no data
Method: Five concentrations tested. Water chemistry determined. Water from Lake Superior. Analytical determination by spectrofluorimetry.
Remark: Call, D.J., L.T., Brooks, N., Ahamd, and J.E., Richter, (1983) Toxicity and metabolism studies with EPA priority pollutants and related chemicals in freshwater organisms, EPA-600/3-83-095, PB83-263665 also report LC50 of 28100 mg/l
Reliability: (2) valid with restrictions
22-MAR-2001
(87)

Type: flow through
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: c = 29400
Method: other
Year: 1986 GLP: no data
Test substance: other TS
Method: Five concentrations tested. Water from Lake Superior. Water chemistry and dissolved oxygen levels determined.
Result: Effects noted at top two concentrations. Most mortality was noted in first 12 hours.
Test substance: Methanol (Burdick & Jackson)
Reliability: (1) valid without restriction
09-MAR-2001
(62)

Type: flow through
 Species: Salmo gairdneri (Fish, estuary, fresh water)
 Exposure period: 96 hour(s)
 Unit: mg/l Analytical monitoring: yes
 LC50: c = 20300
 Method: other
 Year: 1985 GLP: no data
 Test substance: other TS
 Method: Five concentrations used. Analytical determination by spectrofluorimeter. Water from Lake Superior. Water chemistry determined as well as dissolved oxygen. Trimmed Spearman Karber statistical method used.
 Result: Effects were noted immediately at two highest concentrations. Most mortality was noted by 3 hours.
 Test substance: Methanol (Burdick & Jackson)
 Reliability: (1) valid without restrictions
 09-MAR-2001
 (62)

Type: semistatic
 Species: Oryzias latipes (Fish, fresh water)
 Exposure period: 96 hour(s)
 Unit: mg/l Analytical monitoring: no
 LC0: c <= 5000 - 5000
 LC50: m = 35000 - 28000
 LC100: c >= 40000 - 40000
 Method: other
 Year: 1985 GLP: no data
 Test substance: Methanol, Junsei Chemical Co.
 Method: 8 levels 0-40,000 ppm. Measurements at 24, 48 72 and 96 hours. Avoidance and embryogenesis (12 day exposure) also evaluated.
 Remark: Method similar to OECD,
 Result: The first results are 96-hour values, the second are 24 hour values. Avoidance was demonstrated at 10,000-20,000 ppm. Effective half lethal dose on embryogenesis -20,000 ppm, tolerance dose - 1000 ppm, Critical toxic dose 30,000 ppm.
 Reliability: (2) valid with restrictions
 09-MAR-2001
 (58)

Type: semistatic
 Species: other
 Exposure period: 96 hour(s)
 Unit: mg/l Analytical monitoring: no
 LC0: c = 4000 - 4000
 LC50: c = 12000 - 13000
 LC100: c = 15000 - 20000
 Method: other
 Year: 1985 GLP: no data
 Test substance: Methanol, Junsei Chemical Co.
 Method: Red sea bream (Pagrus major) was the test organism used in this test. Eleven test levels were used (0-40,000 ppm).

Remark: Measurements were also conducted at 24, 48 and 72 hours
Reliability: Limited data. Method similar to OECD,
16-MAR-2001 (2) valid with restrictions
(58)

Type: semistatic
Species: other
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC0: c = 4000 - 4000
LC50: c = 12000 - 13000
LC100: c = 15000 - 20000
Method: other
Year: 1985 GLP: no data
Test substance: other TS
Method: Red sea bream (*Pagrus major*) used in test. Eleven levels
(0-40000) used. Measurements also conducted at 24, 48 and 72
hours. Avoidance testing also conducted.
Result: First value is the 96-hour value, the second is the 24 hour
value. Avoidance was demonstrated between 10,000 - 20,000
ppm.
Test substance: Methanol, Junsei Chemical Co.
Reliability: (2) valid with restrictions
09-MAR-2001
(58)

Type: semistatic
Species: other
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC0: c = 5000 - 1200
LC50: c = 13000 - 25000
LC100: c = 20000 - 40000
Method: other
Year: 1985 GLP: no data
Test substance: other TS
Method: Tiger shrimp (*Penaeus japonicus*) used in test. Eight levels
were used (0-40000 ppm). Test design similar to OECD.
Measurements also at 24, 48 and 72 hours. Avoidance testing
also conducted.
Result: First value is 96-hour value, the second value is 24 hour
value. Avoidance demonstrated at 5000 ppm
Test substance: Methanol, Junsei Chemical Co.
Reliability: (2) valid with restrictions
09-MAR-2001
(58)

Type: semistatic
Species: other
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC0: c = 2000 - 10000

LC50: c = 15000 - 30000
 LC100: c >= 40000 - 40000
 Method: other
 Year: 1985 GLP: no data
 Test substance: Methanol, Junsei Chemical Co.
 Method: 8 levels 0-40,000 ppm. Measurements at 24, 48, 72, and 96 hours. Ear shell (*Haliotis discus hannii*) which is a young shell fish was used.
 Remark: Method was similar to OECD
 Result: First value is the 96-hour value, the second is 24-hour value.
 Reliability: (2) valid with restrictions
 22-MAR-2001
 (58)

Type: static
 Species: *Alburnus alburnus* (Fish, estuary)
 Exposure period: 96
 Unit: mg/l Analytical monitoring: no data
 LC50: c = 28000
 Method: other
 Year: 1984 GLP: no data
 Test substance: no data
 Method: A natural brackish water from Baltic sea was used. Water Chemistry was determined, 2 replicates, 10 fish per replicate. Number of concentrations tested unknown.
 Reliability: (2) valid with restrictions
 22-MAR-2001
 (12)

Type: static
 Species: *Pimephales promelas* (Fish, fresh water)
 Exposure period: 96 hour(s)
 Unit: mg/l Analytical monitoring: no
 LC50: c > 100
 Method: other
 Year: 1985 GLP: no data
 Test substance: no data
 Method: Water from Lake Ontario. Test concentrations used 0, 1, 10 And 100 mg/l. Ten fish per replicate. Also tested pillbugs, daphnia magna, flatworms, side swimmers and the segment worm at same concentrations.
 Remark: A screening test with 100 mg/l the highest concentration tested.
 Result: The 96 hour LC50 was greater than 100 mg/l for all test organisms.
 Reliability: (2) valid with restrictions
 09-MAR-2001
 (33)

Type: static
 Species: other
 Exposure period: 96 hour(s)
 Unit: mg/l Analytical monitoring: no data

LC50: c = 12000
 Method: other
 Year: 1984 GLP: no data
 Test substance: no data
 Method: Nitocra spinipes used as test organism. Water chemistry determined. Water use was natural brackish water from the Baltic sea. Number of concentration tested unknown.
 Reliability: (1) valid without restriction
 09-MAR-2001
 (12)

Type: other
 Species: Lepomis macrochirus (Fish, fresh water)
 Exposure period: 96 hour(s)
 Unit: mg/l Analytical monitoring: no
 LC50: c = 29.4
 Method: other
 Year: 1985 GLP: no data
 Test substance: no data
 Reliability: (2) valid with restrictions
 14-MAR-2001
 (50)

4.1 Acute/Prolonged Toxicity to Fish (Added Remarks)

Remark: A summary of acute toxicity data (Appendix B Table B-1) shows a range of LC50 values for fish range from 1,400 to 41,000 mg/l. A QSAR calculation of the a 96 hour LC50 for salt water fish gives a value of 572 mg/l, while the value for freshwater fish and Mysid shrimp is > 1000 mg/l
 21-MAR-2001
 (31)

Remark: Methanol is sometimes used as a carrier solvent in aquatic toxicology studies. Therefore, numerous chronic toxicity tests have, in fact, been conducted with methanol. For instance, both the USEPA TSCA fish bioconcentration test protocol (40 CFR 797.1560) and the ASTM standard guide for conducting early life-stage toxicity tests with fishes (ASTM E1241-92) specifically allow methanol as a carrier solvent at concentrations not to exceed 0.1 ml/L (100 mg/L).
 21-MAR-2001

Remark: Acute toxicity is directly related to the octanol-water partition coefficient; as log OW increases, toxicity increases (e.g., LC50 decreases). Therefore, neutral compounds with low octanol-water partition coefficients, such as methanol, have very low acute toxicity. Acute toxicity via narcosis is generally reversible. In fish, narcosis produces a specific series of behavioral stages including loss of reaction to external stimuli; loss of equilibrium; a decline in respiratory rate; and finally,

21-MAR-2001
(72)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Artemia salina (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC0: c > 10000
Method: other
Year: 1974 GLP: no
Test substance: no data
Method: Concentrations tested (100, 1,000 and 10,000 mg/l). Endpoint evaluated was death.
Reliability: (1) valid without restriction
09-MAR-2001
(63)

Type: static
Species: Ceriodaphnia dubia (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: c = 11
Method: other
Year: 1993 GLP: no data
Test substance: no data
Remark: The LC50 (48 hrs) for freshwater mussel (*Anadonta imbecilis*) was also determined in this study (37.02 mg/l).
Reliability: (1) valid without restriction
14-MAR-2001
(44)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC0: c > 10000
Method: other
Year: 1988 GLP: no data
Test substance: no data
Method: Method DIN 38412. Concentrations tested (0-10000 ppm). Immobilization endpoint evaluated. Water chemistry determined.
Remark: For similar study see Calleja, M.C., G. Persoone, and P.Gead, (1994), Comparative acute toxicity of the first 50 multicentre evaluations of in vitro cytotoxicity chemicals to aquatic non-vertebrates. Arch. Environ. Contam. Toxicol. 26, 69 - 78 The L(E)C50 for methanol in Daphnia Magna was reported as 668,000 umol/l).
Reliability: (1) valid without restriction
09-MAR-2001
(47)

Type: static
Species: Nitocra spinipes (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: c = 12000
Method: other
Year: 1984 GLP: no data
Test substance: no data
Method: A natural brackish water from Baltic sea was used. Water chemistry was determined.
Reliability: (1) valid without restrictions
09-MAR-2001
(12)

4.2 Acute Toxicity to Aquatic Invertebrates (Added Remarks)

Remark: Acute toxicity data for methanol in invertebrates were summarized in an Environ Corporation (1996) report in appendix B, table B-2. The measured LC50 values and median effect concentrations (EC50 values) for immobilization in invertebrate range from 10,000 to 38,000 mg/L. The calculated QSAR 48 hour LC50 is greater than 1000 mg/l.
21-MAR-2001
(32)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Chlorella pyrenoidosa (Algae)
Endpoint: growth rate
Exposure period: 14 day
Unit: mg/l Analytical monitoring: no
NOEC: c = 4% v/v
LOEC: c < 4% v/v
EC50: m < 3.6% v/v = 28.44 g/l
Method: other
Year: 1988 GLP: no data
Test substance: no data
Reliability: (2) valid with restrictions
13-MAR-2001
(81)

Species: Phaeodactylum tricornutum (Algae)
Endpoint: other
Exposure period: 840 hour(s)
Unit: mg/l Analytical monitoring: no
NOEC: c > 100
LOEC: c > 100
EC50: c = 600
Method: OECD Guideline 201 "Algae, Growth Inhibition Test"
Year: 1985 GLP: no

Test substance: no data
Reliability: (1) valid without restrictions
13-MAR-2001
(57)

Species: Phaeodactylum tricornutum (Algae)
Endpoint: other
Exposure period: 35 day
Unit: mg/l Analytical monitoring: no data
LOEC: c 1000
EC50: m = 600
Method: other
Year: 1985 GLP: no data
Test substance: no data
Remark: Study was conducted to evaluate the effect of methanol on
alga reproduction according to report
Reliability: (2) valid with restrictions
08-MAR-2001
(56)

4.3 Toxicity to Aquatic Plants e.g. Algae (Added Remarks)

Remark: A summary table of acute toxicity data for methanol in
Aquatic plants is found in Appendix B, Tables B-3 of the
Environ Corporation (1996) report. Adverse effects
mortality, growth inhibition) occurred when methanol exposures
were in excess of 1,000 mg/L. The calculated QSAR 96 hour
EC50 for green algae was greater than 1000 mg/l
21-MAR-2001
(32)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 5628 mg/kg bw
Method: other
Year: 1994 GLP: no data
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the

Reliability: results are similar in all studies.
21-MAR-2001 (2) valid with restrictions
(67)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 9100 mg/kg bw
Method: other
Year: 1943 GLP: no
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (2) valid with restrictions
21-MAR-2001
(91)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 9540 mg/kg bw
Method: other
Year: 1972 GLP: no
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (2) valid with restrictions
21-MAR-2001
(90)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 11520 mg/kg bw
Method: other
Year: GLP: no data
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.

Reliability: (2) valid with restrictions
21-MAR-2001
(85)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 12750 mg/kg bw
Method: other
Year: 1967 GLP: no
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (2) valid with restrictions
21-MAR-2001
(25)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 12880 mg/kg bw
Method: other
Year: 1941 GLP: no
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (4) not assignable
21-MAR-2001
(77)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 5065 mg/kg bw
Method: other
Year: 1961 GLP: no
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.

Reliability: (2) valid with restrictions
21-MAR-2001
(9)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 7914 mg/kg bw
Method: other
Year: 1975 GLP: no data
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (2) valid with restrictions
21-MAR-2001
(10)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 12900 mg/kg bw
Method: other
Year: 1948 GLP: no
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (2) valid with restrictions
21-MAR-2001
(28)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 10300 mg/kg bw
Method: other
Year: 1971 GLP: no data
Test substance: no data
Remark: LD50 listed is for young adult rat. LD50 for 14 day old rat
= 5861 mg/kg bw and 6970 mg/kg bw for old adult rat.

Reliability: (2) valid with restrictions
12-MAR-2001
(45)

Type: LD50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 7300 mg/kg bw
Method: other
Year: 1994 GLP: no data
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (2) valid with restrictions
21-MAR-2001
(67)

Type: LD50
Species: mouse
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 5800 mg/kg bw
Method: other
Year: 1969 GLP: no
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (2) valid with restrictions
21-MAR-2001
(20)

Type: LD50
Species: mouse
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 14390 mg/kg bw
Method: other
Year: 1971 GLP: no data
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.

Reliability: (2) valid with restrictions
21-MAR-2001
(76)

Type: LD50
Species: rabbit
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 14400 mg/kg bw
Method: other
Year: 1972 GLP: no data
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (2) valid with restrictions
21-MAR-2001
(54)

Type: LD50
Species: dog
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 8000 mg/kg bw
Method: other
Year: 1997 GLP: no data
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (2) valid with restrictions
21-MAR-2001
(93)

Type: LD50
Species: dog
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 7500 mg/kg bw
Method: other
Year: 1994 GLP: no data
Test substance: no data
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Reliability: (2) valid with restrictions

21-MAR-2001
(67)

Type: LD50
Species: miniature swine
Strain: other
Sex: female
Number of
Animals: 3
Vehicle: no data
Value: > 5000 mg/kg bw
Method: other
Year: 1993 GLP: no data
Test substance: other TS
Remark: Details of the study maybe lacking in some areas, but the
results are similar in all studies.
Test substance: Methanol - HPLC grade Sigma Chemical
Reliability: (1) valid without restriction
21-MAR-2001
(29)

Type: LD50
Species: monkey
Strain:
Sex:
Number of
Animals:
Vehicle:
Value: = 7000 - 9000 mg/kg bw
Method: other
Year: 1961 GLP: no
Test substance: no data
Remark: Monkeys receiving methanol doses higher than 3000 mg/kg by
gavage show ataxia, weakness and lethargy within a few hours
of exposure These signs tended to disappear within 24 hours
and were followed by transient coma in some of the animals.
Details are lacking in some areas, but are
similar to other studies.
Reliability: (2) valid with restrictions
21-MAR-2001
(23)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Exposure time: 1 hour(s)

Value: = 145000 ppm
Method: other
Year: GLP: no data
Test substance: no data
Remark: Details are lacking in some areas, but the result is similar in all studies.
Test condition: Exposure was head only.
Reliability: (2) valid with restrictions
22-MAR-2001
(30)

Type: LC50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: = 64000 ppm
Method: other
Year: 1994 GLP: no data
Test substance: no data
Remark: Details are lacking in some areas, but the result is similar in all studies.
Reliability: (2) valid with restrictions
22-MAR-2001
(67)

Type: LC50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: = 73000 ppm
Method: other
Year: 1982 GLP: no data
Test substance: no data
Remark: Details are lacking in some areas, but the result is similar in all studies.
Reliability: (2) valid with restrictions
22-MAR-2001
(76)

Type: LC50
Species: rat
Strain:
Sex:
Number of
Animals:

Vehicle:
Exposure time: 4 hour(s)
Value: = 98600 ppm
Method: other
Year: 1980 GLP: no data
Test substance: no data
Remark: Details are lacking in some areas, but the result is similar in all studies.
Reliability: (2) valid with restrictions
14-MAR-2001
(11)

Type: LC50
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Exposure time: 6 hour(s)
Value: = 67300 ppm
Method: other
Year: 1980 GLP: no data
Test substance: no data
Remark: Details are lacking in some areas, but the result is similar in all studies.
Reliability: (2) valid with restrictions
22-MAR-2001
(11)

Type: other
Species: rat
Strain:
Sex:
Number of
Animals:
Vehicle:
Exposure time: 8 hour(s)
Value: = 64000 ppm
Method: other
Year: GLP: no
Test substance: no data
Remark: Details are lacking in some areas, but the result is similar in all studies.
Test condition: Most likely saturated vapor exposure.
Reliability: (2) valid with restrictions
22-MAR-2001
(78)

Type: LC50
Species: mouse
Strain:
Sex:
Number of

Animals:
 Vehicle:
 Exposure time: 6 hour(s)
 Value: = 41000 ppm
 Method: other
 Year: 1979 GLP: no data
 Test substance: no data
 Remark: Details are lacking in some areas, but the result is similar
 in all studies.
 Reliability: (2) valid with restrictions
 22-MAR-2001
 (73)

Type: LC50
 Species: mouse
 Strain:
 Sex:
 Number of
 Animals:
 Vehicle:
 Exposure time: 134 minute(s)
 Value: = 61100 ppm
 Method: other
 Year: 1994 GLP: no data
 Test substance: no data
 Remark: Details are lacking in some areas, but the rresult is
 similar in all studies.
 Reliability: (2) valid with restrictions
 14-MAR-2001
 (88)

Type: LC50
 Species: cat
 Strain:
 Sex:
 Number of
 Animals:
 Vehicle:
 Exposure time: 4.5 hour(s)
 Value: = 65700 ppm
 Method: other
 Year: 1994 GLP: no data
 Test substance: no data
 Remark: Details are lacking in some areas, but the result is similar
 in all studies.
 Reliability: (2) valid with restrictions
 22-MAR-2001
 (88)

Type: LC50
 Species: cat
 Strain:
 Sex:

Number of
 Animals:
 Vehicle:
 Exposure time: 6 hour(s)
 Value: = 23600 ppm
 Method: other
 Year: 1994 GLP: no data
 Test substance: no data
 Remark: Details are lacking in some areas, but the result is similar
 in all studies.
 Reliability: (2) valid with restrictions
 22-MAR-2001
 (88)

Type: LC50
 Species: cat
 Strain:
 Sex:
 Number of
 Animals:
 Vehicle:
 Exposure time:
 Value: = 20000 - 36900 ppm
 Method: other
 Year: 1931 GLP: no
 Test substance: no data
 Remark: Details are lacking in some areas, but the result is similar
 in all studies.
 Reliability: (2) valid with restrictions
 22-MAR-2001
 (94)

5.1.3 Acute Dermal Toxicity

Type: LD50
 Species: rabbit
 Strain:
 Sex:
 Number of
 Animals:
 Vehicle:
 Value: = 15840 mg/kg bw
 Method: other
 Year: 1994 GLP: no data
 Test substance: no data
 Reliability: (2) valid with restrictions
 12-MAR-2001
 (67)

Type: other
 Species: rabbit
 Strain:
 Sex:
 Number of
 Animals:
 Vehicle:
 Value:
 Method:
 Year: GLP:
 Test substance:
 Remark: In a study in rabbits conducted according to OECD guideline
 404 methanol was classified as non-irritating to the skin,
 but an irritant to the eye (OECD guideline 405).
 Reliability: (1) valid without restrictions
 22-MAR-2001
 (43)

5.4 Repeated Dose Toxicity

Species: rat Sex: male/female
 Strain: Sprague-Dawley
 Route of admin.: inhalation
 Exposure period: 6 hours/day
 Frequency of
 treatment: 5 days/week for 4 weeks
 Post. obs.
 period: none
 Doses: 0, 500, 2000, 5000 ppm
 Control Group: yes, concurrent vehicle
 NOAEL: >= 3000 ppm
 LOAEL: = 5000 ppm
 Method: other
 Year: 1987 GLP: yes

Test substance: other TS
Method: The study used 5 rats /sex/ group. Parameters evaluated included, ophthalmoscopic exam, body weight, clinical signs, organ weights, histopathology and survival
Remark: A good screening study. Daily exposure was 6 hours per day, the normal daily exposure length for inhalation studies evaluating potential workplace exposure.
Result: Actual exposure 0, 520, 1980 and 5010 ppm. All animals survived. In rats nasal and eye discharge (mucoid, nasal, red nasal, lacrimation) was noted in the treatment groups. Only mucoid nasal discharge appeared to be dose related. There was no treatment-related effects on body weight. No ocular abnormalities were noted at the terminal ophthalmoscopic exam. No treatment related histopathological effects (35 tissues) were noted, but spleen weights were increased in female rats exposed at 2,000 ppm (not at 5,000 ppm). No other organ weight effects were noted.
Test substance: Methanol from Celanese Corporation 99.85% pure
Conclusion: Rats were exposed to up to 5,000 ppm (6 hr/d, 5d/wk for 4 weeks) showed no treatment related histopathological effects. Inhalation exposure resulted in some slight treatment-related signs of nasal irritation in rats exposed at 5,000 ppm. No effects were noted in the ophthalmoscopic exam. Overall the results support the use of the present TLV for methanol
Reliability: (1) valid without restriction
14-MAR-2001
(4)

Species: rat Sex: male/female
Strain: Fischer 344
Route of admin.: inhalation
Exposure period: 20 hours/day
Frequency of treatment: daily for 1 year
Post. obs. period: none
Doses: 0, 10, 100, 1000 ppm
Control Group: yes
NOAEL: >= 100 ppm
LOAEL: = 1000 ppm
Method: other
Year: 1986 GLP: no data
Test substance: Methanol, Junsei Chemical Co.
Method: This study used 20/sex per group. Parameters evaluated body weight, food consumption, clinical signs, hematology, organ weight, histopathology, clinical chemistry, and survival.
Remark: This chronic inhalation study design was similar to standard chronic studies in rats except the length of the daily exposure was much longer than normal (20 vs 6 hrs). The design offered little time for normal clearance from the body as exposure was essentially continuous (not normal for industrial exposure or consumer use).
Result: In both males and females exposed at 1,000 ppm a slight decrease in body weight gain was noted at the end of 12

months. Rats exposed at all levels showed no clinical signs or clinical chemistry effects, but increase in liver and spleen weights was noted in female rats (less than 5%). At 100 ppm and lower, no pathological changes due to treatment were noted. One rat died and one was sacrificed during the study (exposure level not indicated). No treatment related effects were reported for food consumption, hematology, antibody test, urinalysis, serum or biochemical tests.

Conclusion: The NOAEL in rats appears to be 100 ppm with only small body weight changes and possible organ weights the only effects seen at in rats exposed at 1,000 ppm

Reliability: (2) valid with restrictions

14-MAR-2001
(58)

Species: rat Sex: male/female
 Strain: Fischer 344
 Route of admin.: inhalation
 Exposure period: 20 hours/day
 Frequency of treatment: daily for two years
 Post. obs. period: none
 Doses: 0, 10, 100, 1000 ppm
 Control Group: yes
 NOAEL: > 100 ppm
 LOAEL: <= 1000 ppm
 Method: other
 Year: 1986 GLP: no data
 Test substance: Methanol, Junsei Chemical Co.
 Method: This study used 52/sex per group. Parameters evaluated body weight, food consumption, clinical signs, hematology, organ weight, histopathology, clinical chemistry, and survival.
 Remark: This carcinogenicity study design was similar to standard carcinogenicity studies in rats except the length of the daily exposure was much longer than normal (20 vs 6 hrs. The design offered little time for normal clearance from the body as exposure was essentially continuous (not normal for industrial exposure or consumer use).
 Result: No treatment related effects were reported for clinical signs, body weight, organ weight food consumption, hematology, antibody test, urinalysis, serum or biochemical tests. A small increase in papillary adenoma of the lung as well as an increase in adenomatosis were the only histopathological changes noted in the high dose males. In the high dose females the incidence of chromaffine cytoma of the adrenal gland was low but slightly higher than the control.
 Conclusion: Although a possible small increase in benign tumors were observed in the high dose animals, methanol is not considered carcinogenic based on the results of this study.
 Reliability: (2) valid with restrictions

14-MAR-2001
(58)

Species: mouse Sex: male/female
 Strain: B6C3F1
 Route of admin.: inhalation
 Exposure period: 20 hours/day
 Frequency of treatment: daily for 18 months
 Post. obs. period: none
 Doses: 0, 10, 100, 1000 ppm
 Control Group:
 NOAEL: > 1000 ppm
 Method: other
 Year: 1986 GLP: no data
 Test substance: Methanol, Junsei Chemical Co.
 Method: Fifty-two per sex per group were studied. Parameters evaluated include clinical signs, organ weight, body weight, food consumption, hematology, urinalysis, histopathology and serum or biochemical tests.
 Remark: This carcinogenicity study design was similar to standard carcinogenicity studies in mice except the length of the daily exposure was much longer than normal (20 vs 6 hrs). The lack of individual data is limitation of this study. The design offered little time for normal clearance from the body as exposure was essentially continuous (not normal for industrial exposure or consumer use).
 Result: No treatment related effects were reported for clinical signs, organ weight, food consumption, hematology, urinalysis, and serum or biochemical tests. Body weight was significantly higher in the high dose group early in the study, but was not different by 12 months. No tumorigenic effects were treatment related.
 Conclusion: Methanol is not considered carcinogenic based on the results of this mouse study.
 Reliability: (2) valid with restrictions
 14-MAR-2001
 (58)

Species: mouse Sex: male/female
 Strain: B6C3F1
 Route of admin.: inhalation
 Exposure period: 20 hours/day
 Frequency of treatment: daily for one year
 Post. obs. period: none
 Doses: 0, 10, 100, 1000 ppm
 Control Group: yes
 NOAEL: >= 100 ppm
 LOAEL: = 1000 ppm
 Method: other

Year: 1986 GLP: no data
 Test substance: other TS
 Method: Thirty mice/sex per group were used in this study. Ten/sex per group sacrificed at 6 months and remainder at 12 months. The parameters evaluated were body weight, food consumption, urinalysis, clinical signs, hematology, histopathology, clinical chemistry and survival.
 Remark: This chronic inhalation study design was similar to standard chronic studies in mice except the length of the daily exposure was much longer than normal (20 vs 6 hrs). The design offered little time for normal clearance from the body as exposure was essentially continuous (not normal for industrial exposure or consumer use). The decrease food consumption and increase in body weight do not make sense.
 Result: In both male and females exposed at 1,000 ppm a statistical significant increase in body weight gain was noted with smaller changes at lower doses at 6 month but no statistical significant effect were noted at 12 months. One mouse died and one was sacrificed during the study (100 ppm). Food consumption was reduced in female mice, but it had no effect on body weight gain. A statistical significant increase in fatty degeneration of the liver in male mice was noted at 1,000 ppm, but fatty livers were noted in all other groups including the control males. No treatment-related effects were reported for, hematology, antibody test, urinalysis, serum or biochemical tests.
 Conclusion: The NOAEL in mice appears to be 100 ppm with a statistical significant increase in body weight gain, fatty livers (males) and decrease in food consumption (females) noted at 1,000 ppm.
 Reliability: (2) valid with restrictions
 14-MAR-2001
 (58)

Species: monkey Sex: female
 Strain: Macaca Fascicularis
 Route of admin.: inhalation
 Exposure period: 21 hours/day
 Frequency of treatment: daily up to 21 days
 Post. obs. period: none
 Doses: 0, 3000, 5000, 7000, 10000 ppm
 Control Group: yes
 NOAEL: = 3000 ppm
 LOAEL: = 5000 ppm
 Method: other
 Year: 1986 GLP: no data
 Test substance: Methanol, Junsei Chemical Co.
 Method: The monkeys were exposed for 21 hrs/ day. Exposure was for 6 days at 10,000 and 7,000 ppm, 14 day at 5,000 ppm, and 21 days at 3,000 ppm. Parameters evaluated included the eye, clinical signs, hematology, histopathology, clinical

chemistry and survival.

Remark: This was a pilot study to set test doses for larger sub-acute inhalation study. The study is useful demonstrating the lack of effect on the eye, CNS effects in a dose related manner and nerve damage at higher doses. The design offered little time for normal clearance from the body as exposure was essentially continuous (not normal for industrial exposure or consumer use).

Result: Monkey exposed at 3,000 ppm methanol showed no adverse effects, but at 5,000 ppm and higher reduced movement, weak knees, involuntary movement, vomiting and dyspnea was reported. No change in clinical chemistry, but slight changes in the central nervous system (hyperplasia of reactive astrocytes in the basal ganglion) were reported at 3,000 ppm. Animals exposed at 5,000 ppm and higher had decreased blood pH (acidosis). The blood methanol level was 526 mg/dl and formic acid 121 mg/dl at 5,000 ppm methanol vs 8 mg/dl methanol and 3 mg/dl at 3000 ppm or lower. Animals exposed at 5,000 ppm had increased neutral lipids (liver function). Degeneration of basal ganglion in the central nervous system and fatty degeneration of the liver were reported in a dose-related manner at 3,000 ppm and higher. Body weight was decreased at 10,000 ppm. One death was reported at day 14 (5,000 ppm). No effects were noted at any test level on the eye or optic nerve.

Conclusion: The minimal effect level in monkey exposed to methanol for 21 hours per day was 3,000 ppm.

Reliability: (2) valid with restrictions

14-MAR-2001
(58)

Species: monkey Sex: female

Strain: Macaca Fascicularis

Route of admin.: inhalation

Exposure period: 21 hours/day

Frequency of treatment: 12, 29, 210 days

Post. obs. period: 12 months

Doses: 1000, 2000, 3000, 5000 ppm

Control Group: no

NOAEL: < 1000 ppm

LOAEL: = 1000 ppm

Method: other

Year: 1986 GLP: no data

Test substance: Methanol, Junsei Chemical Co.

Method: The study used 3 monkeys /group, except 2/group at 5,000 ppm. The daily exposure was 21 hrs/ days. Exposure was for 12 days at 5,000 ppm, 20 days for 2,000 and 3,000 ppm, and 7 months for 1,000 ppm. Recovery periods were for 1, 4, 6, 12 months. Parameters evaluated included eyes, body weight, clinical signs, hematology, histopathology, clinical chemistry and survival.

Remark: This inhalation study had a complex design. No

control group was used. The design offered little time for normal clearance from the body as exposure was essentially continuous (not normal for industrial exposure or consumer use).

Result: Monkeys exposed at 1,000, 2,000 and 3,000 ppm methanol showed no clinical signs, but at 5,000 ppm reduced movement, weak knees, involuntary movement, vomiting and dyspnea was reported. No changes in body weight, temperature, or ECG were reported in any group. No clinical chemistry, but slight changes in the nervous system were reported at 1,000 ppm. Animals exposed at 2,000 ppm and higher had decreased blood pH (acidosis), and increased GTP. Changes in blood pH return to normal during the recovery period. Pathological changes in the central nervous system were reported in a dose-related manner at 1,000 ppm and higher. One death was reported at day 5 (5,000 ppm). Slight partial atrophy of the optic nerve was noted at 3,000 ppm and higher, but it was questionable if it was due to treatment or not.

Conclusion: The minimal effect level in monkey exposed to methanol for 21 hours per day for up to 7 months was 1,000 ppm.

Reliability: (2) valid with restrictions

14-MAR-2001

(58)

Species: monkey Sex: male/female

Strain: Macaca Fascicularis

Route of admin.: inhalation

Exposure period: 6 hours/day

Frequency of treatment: 5 days/week for 4 weeks

Post. obs. period: none

Doses: 0, 500, 2000, 5000 ppm

Control Group: yes, concurrent vehicle

NOAEL: > 5000 ppm

Method: other

Year: 1987 GLP: yes

Test substance: other TS

Method: The study used 3 monkeys /sex/ group. Parameters evaluated included, ophthalmoscopic exam, body weight, clinical signs, organ weights, histopathology and survival

Remark: A good screening study. Daily exposure was 6 hours / day the normal daily exposure length for inhalation studies evaluating potential workplace exposure.

Result: Actual exposure 0, 520, 1980 and 5010 ppm. All animals survived. No clinical signs were noted in monkeys. There was no treatment related effects on body weight. No ocular abnormalities were noted at the terminal ophthalmoscopic exam. No treatment related histopathological effects (35 tissues) were noted, but spleen weights were increased in the high dose female monkeys. No other organ weight effects were noted.

Test substance: Methanol from Celanese Corporation 99.85% pure

Conclusion: Monkeys were exposed to up to 5,000 ppm (6 hr/d, 5d/wk for 4 weeks) showed no treatment related effects, including the

ophthalmoscopic exam. Overall the results support the use of the present TLV for methanol

Reliability: (1) valid without restriction
14-MAR-2001
(4)

Species: monkey Sex: female
Strain: Macaca Fascicularis
Route of admin.: inhalation
Exposure period: 22 hours/day
Frequency of treatment: 7 days/week for 2.5 years
Post. obs. period: none
Doses: 0, 10, 100, 1000 ppm
Control Group: yes
NOAEL: <= 10 ppm
LOAEL: = 10 ppm
Method: other
Year: 1986 GLP: no data
Test substance: Methanol, Junsei Chemical Co.
Method: There were 8 female monkey/group, except for 2/group at 5,000 ppm. Sacrifices were conducted 7 month (2/group), 19 month (3/group), and at 30- month (3/group). Parameter evaluated included eye, body weight, clinical signs, hematology, histopathology, clinical chemistry and survival.
Remark: The design offered little time for normal clearance from the body as exposure was essentially continuous (not normal for industrial exposure or consumer use).
Result: Monkeys exposed at all level showed no clinical effects, but slight pathological changes in the nervous system (hyperplasia of reactive astroglia in the white matter) and liver (fatty degeneration) were noted at the seven month sacrifice). Slight blood changes were noted at 7 months in the blood in all but the 10-ppm group. In the 1000 ppm monkeys slightly abnormal ECG and blood pH were reported at 7 months. At the 19-month sacrifice the same nervous system and liver effects reported at 7 months were noted. At the final sacrifice hyperplasia of reactive astroglia (white matter) and liver (fatty degeneration) effects were noted all groups but the effect was less in the 10 and 100-ppm monkeys. The nervous system effects were thought to be transient and reversible after exposure was terminated, because no correlation with dose level, period of exposure and the magnitude of the effect. Slight liver and kidney effects were seen at 1000ppm and kidney effects only at 100 ppm
Conclusion: The minimal effect level in monkey exposed to methanol for 22 hours per day for up to 7 months was 10 ppm. Repeated exposure may lead to transient pathological effects on the central nervous system.
Reliability: (2) valid with restrictions
14-MAR-2001
(58)

Species: rats Sex: male/female
 Strain: Sprague-Dawley
 Route of admin.: gavage
 Exposure period: 90 days
 Frequency of treatment: daily
 Post. obs. period:
 Doses: 0, 100, 500, 2500 mg/kg bw
 Control Group: yes
 NOAEL: > 500 mg/kg bw
 LOAEL: = 2500 mg/kg bw
 Method: EPA
 Year: 1986 GLP: no data
 Test substance: Methanol
 Method: The U.S. EPA Office of Solid Waste sponsored a 90-day subchronic testing of methanol in Sprague-Dawley rats (30/sex/dose). Six weeks after dosing, 10 rats/sex/dose group were sacrificed, the remaining rats were sacrificed at 90 days.
 Remark: There were no differences between dosed animals and controls in body weight gain, food consumption, gross or microscopic evaluations. Elevated levels of SGPT, SAP, and increased, but not statistically significant, liver weights in both male and female rats suggest possible treatment-related effects in rats dosed with 2500 mg methanol/kg/day despite the absence of any histopathologic lesions in the liver. Brain weights in high-dose group males and females were significantly less than those of the control group.
 Conclusion: Based on these findings, 500 mg/kg/day of methanol is considered a NOAEL in rats
 Reliability: (2) valid with restrictions
 22-MAR-2001
 (86)

5.4 Repeated Dose Toxicity (Added Remarks)

Remark: In a limited study, Sprague Dawley rats were exposed to airborne methanol concentrations of 200, 2,000 or 10,000 ppm for 6 hours per day, 5 days per week for as long as six weeks. This caused no signs of lung inflammation or irritation. Histologic analyses of lung tissue were not conducted.
 22-MAR-2001
 (92)

Remark: In an old Russian study, rabbits exposed to 61 mg/m³ (~50 ppm) methanol for six months (duration of exposure per day not given) were reported to have ultrastructural changes in the photoreceptor cells and Mueller fibers. Not enough information to be useful.
 22-MAR-2001
 (21)

Remark: Two dogs were exposed to about 13,000 mg/m³ (10,000 ppm) methanol for about three minutes at hourly intervals eight times daily for 100 days, a total of 800 brief exposures. Both dogs were reported to have survived the exposure and exhibited no symptoms or unusual behavior or visual toxicity attributable to methanol poisoning. Old, of little value.

22-MAR-2001
(71)

Remark: In an old study exposed four dogs were exposed to airborne concentrations of methanol from 585 to 650 mg/m³, eight hours per day, seven days per week for 379 days in a continuously ventilated chamber. Hematological determinations and ophthalmoscopic examinations were conducted. No adverse effects of any kind were reported. Old, of little value.

22-MAR-2001
(70)

Remark: In a old russian study rats received oral doses of 10, 100, or 500 mg/kg/ day for one month and were reported to show liver changes characterized by focal proteinic degeneration of hepatocytic cytoplasm. Old, of little value.

22-MAR-2001
(75)

Remark: Methanol was used as a solvent in an oral lifetime drinking water study of malonaldehyde in swiss mice. Three different levels of methanol were used in drinking water as controls (0.222, 0.444, 0.889%). The only effect noted was a reported increase in lymphomas in the two highest levels of methanol treated mice. The incidence rate of lymphomas was within historical control for the lab. An evaluation of a lifetime exposure to methanol by the oral route.

22-MAR-2001
(5)

Remark: Methanol was used as a solvent in a dermal study in hairless mice exposed topically to retinoic acid in methanol. The treatment was daily for 30 weeks. At the end of 55 weeks no skin tumors were noted in the methanol-only treated animals and no treatment related effects on the skin were noted. An evaluation of a chronic exposure to methanol by the dermal route.

22-MAR-2001
(1)

Remark: Methanol was used as a solvent in a life time skin painting study of malonaldehyde in swiss mice. The mice were treated 3 times a week with a dose of 0.05 ml of methanol. No treatment related effects on the skin, including skin tumors were noted. An evaluation of a lifetime exposure to methanol by the dermal route.

22-MAR-2001
(5)

5.5 Genetic Toxicity 'in Vitro'

Type:	Ames test
System of	
testing:	TA 98, TA100, TA1535, TA1537, TA1538, WP2uvrA
Concentration:	5, 10, 50, 100, 5000, 1000, 5000 ug/plate
Cytotoxic Conc.:	none
Metabolic	
activation:	with and without
Result:	negative
Method:	other
Year:	1985
	GLP: no data
Test substance:	other TS
Remark:	See: DeFlora S.: (1982) Study of 106 organic and inorganic compounds in Salmonella/microsome test. Carcinogenesis, 2, 283-298. Methanol not active in TA98, TA100, TA1635, TA1537 or TA1538 with or without activation.
Test substance:	Methanol-Wacko Pure Chemical Industry
Conclusion:	Methanol is not mutagenic in this assay.

Reliability: (2) valid with restrictions Reliability
15-MAR-2001
(74)

Type: Cytogenetic assay
System of testing: Chinese hamster
Concentration: 0, 7, 1, 14.3, 28.5 mg/ml
Cytotoxic Conc.: 28.5 mg/ml inhibit cell growth by 50%.
Metabolic activation: with and without
Result: negative
Method: other
Year: 1983 GLP: no data
Test substance: Methanol, Junsei Chemical Co.
Method: Methanol was dissolved in culture medium with or without 10% serum. Rats S9 was used for metabolic activation. Don cells from lung of Chinese hamster were used in this study. 200 chromosome were checked per dose level. Cells evaluated at 6, 24 and 48 hours after treatment.
Remark: Methanol produced an increase in SCE without metabolic activation at 28.5 mg/ml.
Result: Methanol did not induce chromosomal aberrations in this test.
Conclusion: Methanol is not mutagenic in this assay.
Reliability: (2) valid with restrictions
15-MAR-2001
(58)

Type: Escherichia coli reverse mutation assay
System of testing:
Concentration: 0. 10, 50, 100, 1000, 5000 ug/plate
Cytotoxic Conc.: none
Metabolic activation: with and without
Result: negative
Method: other
Year: 1983 GLP: no data
Test substance: Methanol, Junsei Chemical Co.
Method: Rat liver S9 was used for metabolic activation.
Result: Methanol did not cause an increase in mutations in E. coli.
Conclusion: methanol is not mutagenic in this assay.
Reliability: (2) valid with restrictions
15-MAR-2001
(58)

Type: Mammalian cell gene mutation assay
System of testing: Chinese hamster V79
Concentration: 0, 15.8, 31.7, 47.4, 63.3 mg/ml
Cytotoxic Conc.: 63.3 mg/ml (inhibit 70%).
Metabolic activation: with and without

Result: negative
 Method: other
 Year: 1983 GLP: no data
 Test substance: Methanol, Junsei Chemical Co.
 Method: Methanol was dissolved in culture medium. Rat liver S9 was used in this test. Cells were treated for 6 days and then evaluated.
 Result: Methanol did not increase frequency of gene mutations in this assay.
 Conclusion: methanol was not mutagenic in this test.
 Reliability: (2) valid with restrictions
 15-MAR-2001
 (58)

Type: Salmonella typhimurium reverse mutation assay
 System of testing:
 Concentration: 0, 10, 40, 100, 1,000, 5000 ug/plate
 Cytotoxic Conc.: none
 Metabolic activation: with and without
 Result: negative
 Method: other
 Year: 1983 GLP: no data
 Test substance: Methanol, Junsei Chemical Co.
 Method: Rat liver S9 was used in this assay. Plates incubated for 2 days at 37C.
 Result: Methanol did not inhibit cell growth or increase the number of reverse mutation colonies.
 Conclusion: Methanol was not mutagenic in this assay.
 Reliability: (2) valid with restrictions
 15-MAR-2001
 (58)

Type: Yeast gene mutation assay
 System of testing: Neurospora crassa
 Concentration: unknown
 Cytotoxic Conc.: unknown
 Metabolic activation: without
 Result: negative
 Method: other
 Year: 1984 GLP: no data
 Test substance: no data
 Reliability: (1) valid without restriction
 15-MAR-2001
 (3)

5.5 Genetic Toxicity 'in Vitro'(Added Remarks)

Remark: The in vitro induction of micronuclei in chinese hamster V79 cell was analyzed after exposure of the cells to 50 ul/ml of ethanol, methanol, butanol or propanol. None of the 4 alcohols induced micronuclei

22-MAR-2001
(48)

Remark: Methanol did induce chromosomal changes in Aspergillus. It did not induce sister chromatic exchanges in Chinese hamster cells in vitro, but caused significant increases in mutation frequencies in L5178Y mouse lymphoma cells.

22-MAR-2001
(95)

Remark: A report of increased mutation frequency in L5178Y mouse lymphoma cells with activation was reported in an abstract

22-MAR-2001
(53)

Remark: Methanol has been reported to show negative results in all in vitro sister chromatid exchange tests, cell transformation assays and Neurospora crassa tests, when assayed without exogenous metabolic activation

22-MAR-2001
(89)

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay
Species: mouse Sex: male
Strain: other
Route of admin.: inhalation
Exposure period: 6 hours. 5 days
Doses: 0, 800, 4000 ppm
Result: negative
Method: other (calculated)
Year: 1990 GLP: no data

Test substance: other TS

Remark: EPA study conducted in a government laboratory.

Result: No genotoxic effects noted (NOAEL(NOEL) (8,000 ppm). No evidence of treatment induced SCE, chromosome aberration or micronucleus in lung cell. No evidence of treatment induced synaptoneal complex damage in spermatocytes. No evidence of treatment induced increased frequencies of micronucleus in blood cells

Test substance: Methanol, 99.9% pure Fisher Scientific

Conclusion: No cytogenetic effects (SCE, CA, Mn) were seen in male mice exposed for 5 days to 400 or 8, 000 ppm methanol (blood cells, lung cell, testicular germ cell).

Reliability: (1) valid without restriction

14-MAR-2001
(19)

Type: Micronucleus assay
Species: mouse Sex: male
Strain: ICR
Route of admin.: gavage
Exposure period: 24 hours
Doses: 1.05, 2.11, 4.21, 8.41 g/kg bw
Result: negative
Method: other
Year: 1983 GLP: no
Test substance: Methanol, Junsei Chemical Co.
Method: Six animals per group were used. Volume of dose was 20 ml/kg. The mice were killed 24 hours after dosing. Bone marrow was taken from the femur and 1000 multi-stationable red blood cells were checked.
Result: Under conditions of the test, methanol didn't cause an increase in micronucleus at any test level , including the LD50
Reliability: (2) valid with restrictions
15-MAR-2001
(58)

5.6 Genetic Toxicity 'in Vivo'(Added Remarks)

Remark: In a gavage study normal and folate deficient mice were given 0, 300, 600, 1200 or 2500 mg/kg of methanol in 4 daily doses. No indication of genotoxic response to methanol was reported in the normal or folate deficient mice
22-MAR-2001
(59)

5.8 Toxicity to Reproduction

Type: Fertility
Species: monkey Sex: female
Strain: no data
Route of admin.: inhalation
Exposure Period: 2.5 hrs
Frequency of treatment: daily - 365 d
Premating Exposure Period
male: none
female: 120 d
Duration of test: 365 d
Doses: 0, 200, 600, 1800 ppm
Control Group: yes
NOAEL Parental: > 1800 ppm
Method: other
Year: 1999 GLP: yes

Test substance: Methanol 99.05 pure, HPLC Fisher Scientific

Method: The study used 11 or 12 female monkeys/per group. Exposure was 2.5 hr/day, 7 days/week before and during pregnancy. Parameters evaluated included body weight, clinical signs, menstrual cycle, timed matings, pregnancy observations and survival. Blood methanol, plasma formate, and serum folate was determined every other week. Delivery exams were conducted on offspring. In addition body weight, clinical signs, and survival were also evaluated.

Remark: . An excellent well conducted study in a species that is more closely associated with humans as far as methanol toxicity is concerned. Study was sponsored by EPA, auto companies and API. Study was reviewed by an outside expert panel, who agreed with the study author's conclusions.

Result: The weights of all females were quite stable during the study. Mean weight gain during pregnancy varied from 1.3 kg to 1.8 kg across all exposure groups. Clinical observations did not indicate the presence of overt toxicity in the adult females, and none exhibited a pattern of responses inductive of fine-motor incoordination due to methanol exposure. Methanol exposures did not affect the size of the offspring at birth, the average birth weight, crown-rump length, and head size of infants in the methanol-exposure groups.

Conclusion: Chronic methanol exposures for up to 1 year did not cause overt maternal toxicity in m. fascicularis females. The the ability of females give birth to healthy live-born infants were also unaffected. Methanol exposures were associated with a reduction in the length of pregnancy (not dose dependent). No decrease in offspring birth size was observed.

Reliability: (1) valid without restriction

14-MAR-2001

(17)

Type: Two generation study

Species: rat Sex: male/female

Strain: Sprague-Dawley

Route of admin.: inhalation

Exposure Period: 20 hr

Frequency of treatment: daily

Premating Exposure Period

male: P= 8-16 wks, F1=0-14 wks, F2=0-8 wks

female: P=8-16 wks, F1=0-21 wks, F2=0-8 wks

Duration of test: 365 days

Doses: 0, 10, 100, 1000 ppm

Control Group: yes

NOAEL Parental: = 100 ppm

NOAEL F1 Offspr.: = 100 ppm

NOAEL F2 Offspr.: = 100 ppm

LOEL parental : = 1000 ppm

LOEL F1 offspring : = 1000 ppm

Method: other

Year: 1985 GLP: no data

Test substance: Methanol, Junsei Chemical Co.

Method: Thirty /sex per group were used in the F0 generation. Observations were made in the F0, F1, and F2 generation. Parameters evaluated included body weight, food consumption, clinical signs, organ weights, histopathology and survival. In the offspring general observation at birth, organ check, organ texture, genital function and movement were evaluated.

Remark: This 2-generation study design was similar to standard 2-generation studies in rats except the length of the daily exposure was much longer than normal (20 vs 6 hrs). The design offered little time for normal clearance from the body as exposure was essentially continuous (not normal for industrial exposure or consumer use).

Result: No treatment related effects were reported for clinical signs, but body weight was decreased after 7 weeks in rats exposed to 1,000 ppm (significant in male, not significant in females). Food consumption was also decreased in the top dose animals. No treatment related effects on sexual cycle, pregnancy, delivery or reproductive capacity was observed. Offspring appeared normal and no histopathological effects were noted. The F1 rats showed no treatment-related effects on body weight, food/ water consumption or general movement. The high dose male offspring had a significant increase in the rate of early descensus testis. Brain weights were statistically significantly reduced in the high dose males and females at 8 weeks of age as well as in males sacrificed at 16 weeks and possible females at 24 weeks. The F2 rats showed no treatment-related effects on body weight, food/ water consumption or general movement. The high dose male offspring had a significant increase in the rate of early descensus testis. Brain, hypophysis and thymus weights were statistically significantly reduced in the 1,000 ppm males and females at 8 weeks of age.

Conclusion: Inhalation exposure had some slight treatment-related effects in rats exposed at 1,000 ppm in a 2-generation study. The effects did not effect reproductive performance. 100 ppm was a NOEL

Reliability: (2) valid with restrictions

14-MAR-2001

(58)

5.8 Toxicity to Reproduction (Added Remarks)

Remark: Mature male rats (Sprague-Dawley) were exposed to methanol concentrations of 200, 2,000, or 10,000 ppm for one, two, four, six weeks and examined them for alteration in circulating free testosterone, lutenizing hormone and follicle stimulating hormone. Significantly decreased levels of circulating free testosterone were observed among rats exposed at 200 ppm for 2 and 6 weeks and 6 weeks at 2,000 ppm. The high dose group (10,000-ppm) showed no change. The authors interpreted this as evidence that methanol exposure had lowered testicular production of testosterone. In addition, significant increases in circulating LH were

observed after six weeks of exposure to 10,000 ppm. No changes in follicle stimulating hormone levels were observed.

Reliability: (2) valid with restrictions
22-MAR-2001
(18)

Remark: The potential toxic effects of methanol vapors on testicular production of testosterone and the morphology of testes were investigated using normal or methanol-sensitive folate-reduced rats. Methanol inhalation at the level of 200 ppm, for up to six weeks (8 hours/day, 5 days/week), did not reduce serum testosterone levels in normal rats. Testes isolated from methanol-exposed (200 ppm) rats had the same capability as those from air-exposed rats in synthesizing testosterone whether testes were incubated in the absence or presence of hCG. The testes-to-body weight ratio of rats exposed up to 800 ppm methanol for up to 13 weeks (20 hours/day, 7 days/week) were not different from those of the air-exposed rats.

Reliability: (2) valid with restrictions
22-MAR-2001
(49)

Remark: Two experiments were conducted to evaluate the acute effects of inhaled methanol on serum hormones associated with reproductive function in the male rat. In the first experiment, rats exposed to methanol (0, 200, 5000 and 10,000 ppm) for 6 hours were killed at the end of the exposure period or the following morning. The effect of the handling associated with placing the rat in the exposure chamber was also evaluated by comparing hormonal changes in sham- and methanol-exposed groups acclimated for two weeks with groups that were not acclimated. Prior handling resulted in an increase in serum lutenizing hormone greater in the non-acclimated groups than in the acclimated group. In the second experiment, groups of acclimated and non-acclimated rats were exposed to 0 or 5000 ppm methanol for 1, 2 and 6 hours and killed immediately after removal from the chamber. Serum lutenizing hormone, testosterone and follicle stimulating hormone values were not different in sham- vs methanol-exposed rats at any time point. As in experiment 1, an effect of prior handling was noted. In general, the concentrations of these hormones and serum prolactin in the non-acclimated rats were greater than those observed for acclimated rats. Methanol exposure resulted in increased prolactin concentrations under both handling conditions

Reliability: (2) valid with restrictions
22-MAR-2001
(24)

5.9 Developmental Toxicity/Teratogenicity

Species: rat Sex: female
 Strain: Sprague-Dawley
 Route of admin.: inhalation
 Exposure period: 7 hours/day
 Frequency of treatment: daily
 Duration of test: day 1-19 of gestation
 Doses: 0, 5000, 10000, 20000 ppm
 Control Group: yes, concurrent vehicle
 NOAEL Maternal Toxicity: ≥ 10000 ppm
 NOAEL Teratogenicity: $= 10000$ ppm
 LOAEL Maternal Toxicity: ≤ 20000 ppm
 LOAEL Teratogenicity : ≤ 20000 ppm
 Method: other
 Year: 1985 GLP: no
 Test substance: Reagent Grade Methanol -Matheson, Coleman & Bell Manuf. Chemists
 Method: Pregnant females, 15 per group, except 13/ group at 5,000 ppm were exposed for 7 hrs/ day, on days 1-19 of gestation. Parameters evaluated included body weight, food consumption, clinical signs, and survival. Blood methanol level, corpora lutea, dead, resorbed, malformed fetuses [half visceral, half skeletal] observations were also made.
 Remark: Different incidences of visceral malformations were reported in the text than were reported in the tables. The occurrence of maternal toxicity in the significantly affected group compromises an interpretation of the teratogenic effects as being solely the result of in utero methanol exposure.
 Result: The highest concentration of methanol produced slight maternal toxicity (unsteady gait) and a high incidence of congenital malformations, predominantly extra or rudimentary cervical ribs and urinary or cardiovascular defects. Blood methanol increased with dose (1.00, 2.24 and 8.65 mg/ml}. The fetal observations that were significantly different from control ($p < 0.05$) at 20,000 ppm are: Number of litters(fetus) with visceral and skeletal malformation, the percentage of litters with abnormal fetuses and the percentage of normal fetus. A non statistical increase in malformation was also reported at 10,000 ppm. No significantly differences from control ($p < 0.05$) was noted at any of the lower doses.
 Conclusion: The highest level of methanol produced slight maternal toxicity and a significant increase in congenital malformations. A non statistical increase in malformation was also reported at 10,000 ppm
 Reliability: (2) valid with restrictions
 15-MAR-2001
 (55)

Species: rat Sex: female
 Strain: Sprague-Dawley
 Route of admin.: inhalation
 Exposure period: 20 hours/day
 Frequency of treatment: daily
 Duration of test: day 7-17 of gestation

Doses: 0, 200, 1000, 5000 ppm
 Control Group: yes
 NOAEL Maternal Toxicity: > 1000 ppm
 NOAEL Teratogenicity: > 1000 ppm
 LOAEL Maternal Toxicity : <= 5000 ppm
 LOAEL Teratogenicity : <= 5000 ppm
 NOAEL Embryotoxicity : >= 1000 ppm
 Method: other
 Year: 1986 GLP: no data
 Test substance: Methanol, Junsei Chemical Co.
 Method: Thirty-six pregnant rats per group were used in this study. Twenty were sacrificed/group at day 20 and 10/group were allowed normal delivery. Parameters evaluated included body weight, food consumption, clinical signs, organ weight, histopathology and survival. The number of fertilized corpus luteum, implantation, living and death fetuses, were also determined. Visceral or skeleton evaluations were conducted on each litter. Offspring from the normal delivery were subjected to general observation at birth, organ check, organ texture, genital function and movement. The F1 were bred and all sacrificed at day 20, litter evaluated as above.
 Remark: Similar to standard teratogenicity study in rats except the length of the daily exposure was much longer than normal (20 vs 6 hrs little time for clearance as exposure was essentially continuous) and some pregnant rats were allowed to deliver normally.
 Result: Dams exposed at 5,000 ppm had decreased rate of body weight gain, decreased food/water consumption, and one death (plus one sacrificed). Increased embryo mortality, decreased fetal weight, increase in septal defects, obstructed vertebro-costal foramen, cervical ribs, excess sublingual foramen nervosa, delayed fetal growth and reduced ossification were noted in the high dose fetuses. In the normal delivery groups decreased food/water consumption, and delayed pregnancy (0.7 days) were reported in the high dose. Pups from the high dose group had increased early mortality, lower birth weights, lower postnatal body weight and a slight decreased water consumption (no effect on food consumption). The high dose male offspring sacrificed at 8 weeks had decreased brain, thyroid, thymus, testes weight and increased in hypophysis weight. The high dose females had reduced brain and thymus weights. No histopathological effects were noted in these organs, except hemilateral thyroid defects
 Conclusion: Inhalation exposure demonstrated treatment-related effects in rats and their fetuses exposed at 5,000 ppm. Fetal toxicity, visceral/skeleton effects were seen in the fetuses exposed at 5,000 ppm , but this dose was maternally toxic. Methanol is not considered teratogenic in this study. 1,000 ppm was a NOAEL for both the dam and the fetus.
 Reliability: (2) valid with restrictions
 15-MAR-2001
 (58)
 Species: mouse Sex: female

Strain: CD-1
 Route of admin.: inhalation
 Exposure period: 7 hours/day
 Frequency of treatment: day 6-15 of gestation
 Duration of test: 20 days
 Doses: 0, 1000, 2000, 5000, 7500, 10000, 15000 ppm
 Control Group: yes
 NOAEL Maternal Toxicity: > 15000 ppm
 NOAEL Teratogenicity: = 1000 ppm
 NOAEL Embryotoxicity : = 1000 ppm
 LOAEL Teratogenicity : = 2000 ppm
 LOAEL Embryotoxicity : = 2000 ppm
 Method: other
 Year: 1993 GLP: no data
 Test substance: Methanol , High purity Optima grade Fisher Scientific
 Method: Blood methanol concentrations were determined on gestation days 6, 10, and 15. Fetus were examined for number of implantation sites, live/dead fetuses, and resorptions. Fetuses were examined externally and weighed as a litter. Half of each litter was examined for skeletal morphology/ Internal soft tissue anomalies.
 Remark: Study design is complex. Only 3 chambers were used and exposures were staggered. Number of animal used appeared to be adequate, but it was hard to tell exact number used, as data was listed as litters per treatment group. Some animals were removed for plasma methanol determinations.
 Result: One dam died in each of the 7,500, 10,000, and 15,000 ppm methanol exposure groups. The methanol exposed dams gained less weight than did unexposed dams fed ad libitum. Significant increases in the incidence of exencephaly and cleft palate were observed at 5,000 ppm and above, increased embryo/fetal death at 7,500 ppm and above (including an increasing incidence of full- litter resorptions), and reduced fetal weight at 10,000 ppm and above. A dose-related increase in cervical ribs or ossification sites lateral to the seventh cervical vertebra was significant at 2,000 ppm and above. Methanol plasma levels increased with dose. No signs of maternal toxicity were noted.
 Conclusion: The NOAEL for the developmental toxicity in this study was 1,000 ppm.
 Reliability: (2) valid with restrictions
 15-MAR-2001
 (66)

Species: mouse Sex: female
 Strain: CD-1
 Route of admin.: inhalation
 Exposure period: 6 hours/day
 Frequency of treatment: 7-9 and day 9-11, day 6-15
 Duration of test: 20 days
 Doses: 0, 5000, 10000, 15000 ppm
 Control Group: yes

NOAEL Maternal Toxicity: >= 10000 ppm
 NOAEL Teratogenicity: = 5000 ppm
 LOAEL Maternal Toxicity : <= 15000 ppm
 LOAEL Teratogenicity : = 10000 ppm
 NOAEL Embryotoxicity : = 5000 ppm
 Method: other
 Year: 1993 GLP: no data
 Test substance: Methanol -HPLC grade J.T. Baker
 Method: The study used 17-27 pregnant mice per group. Parameters evaluated include body weight, clinical signs, and survival. The number of live/ dead fetuses, resorbed, and malformed fetuses[visceral] plus implant sites was also determined.
 Remark: A pilot study was also reported in this paper that was used to set conditions for the main study. A good special study that examined certain time periods during gestation and the effect of methanol on neural tube defects.
 Result: Neurological effects (ataxia, depressed motor activity circling, tilted heads) were noted in the 15,000 ppm dams only on days 1,2 and 3 of exposure (20, 10, 5%). Maternal body weights were decreased at day 17 at 15,000 ppm (high resorptions). Embryotoxicity was noted in fetuses (increased resorptions, reduced fetal weights, and/or fetal malformations) at 10,000 and 15,000 ppm level, while no observable adverse effects were seen in the 5,000 ppm group. Neural and ocular defects, cleft palate, hydronephrosis, deformed tails, and limb (paw and digit) anomalies were reported. Neural tube defects and ocular lesions occurred after methanol inhalation between GD 7-9, while limb anomalies were induced only during GD 9-11, cleft palate and hydronephrosis were observed after exposure during either period.
 Conclusion: The highest level of methanol (15,000 ppm) produced slight maternal toxicity and embryotoxicity. Teratogenicity and embryotoxicity was also reported at 10,000 ppm, but not 5,000 ppm.
 Reliability: (2) valid with restrictions
 15-MAR-2001
 (13)
 Species: monkey Sex: female
 Strain: Macaca Fascicularis
 Route of admin.: inhalation
 Exposure period: 2.5 hours/day
 Frequency of treatment: daily
 Duration of test: 120 days
 Doses: 0, 200, 600, 1800 ppm
 Control Group: yes, concurrent vehicle
 NOAEL Maternal Toxicity: > 1800 ppm
 NOAEL Teratogenicity: > 1800 ppm
 Method: other
 Year: 1999 GLP: no data
 Test substance: Methanol , High purity HPLC grade Fisher Scientific
 Method: Eleven or 12 female monkey per group were used in this study. Pregnancy observations and delivery exam were conducted. In addition body weight, clinical signs, and survival were also

evaluated.

Remark:

An excellent well conducted study in a species that is more closely associated with humans as far as methanol toxicity is concerned. Study was sponsored by EPA, auto companies and API. Study was reviewed by an outside expert panel, who agreed with the study author's conclusions.

Result:

The weights of all females were quite stable during the study. Mean weight gain during pregnancy varied from 1.3 kg to 1.8 kg across all exposure groups. Clinical observations did not indicate the presence of overt toxicity in the adult females, and none exhibited a pattern of responses indicative of fine-motor incoordination due to methanol exposure. Methanol exposures were associated with a reduction in the length of pregnancy, thus shortening the gestation period of the offspring, but did not affect the size of the offspring at birth, the average birth weight, crown-rump length, and head size of infants in the methanol-exposure groups. Neurobehavioral testing suggested possible effects in two tests, but the effects was not concentration dependant or a significant overall effect across the methanol groups. Another observation, not judged a treatment related effect, was a serve wasting syndrome in two female offspring in the high dose methanol group. These two observations were not considered to be treatment related.

Conclusion:

Chronic methanol exposures for up to 1 year did not cause overt maternal toxicity in *m. fascicularis* females. Methanol exposures were associated with a reduction in the length of pregnancy (not dose dependent). No decrease in offspring birth size was observed. No obvious birth defects were noted.

Reliability:

15-MAR-2001

(16)

(1) valid without restriction

5.9 Developmental Toxicity/Teratogenicity (Added Remarks)

Remark:

Rats were dosed by gavage during Days 1-8 of pregnancy at 0, 1.6, 2.4, or 3.2 g methanol/kg/day. Animals were killed on Days 9, 11, or 20 of pregnancy, and maternal, embryonic, or fetal parameters were assessed. No treatment related effect on estradiol, progesterone, lutenizing hormone and prolactin was observed. Reductions in pregnant uterine and implantation site weights were seen on Day 9, but no effects on embryo/fetal survival or development were noted. The 3.2 g/kg/day dose of methanol produced a reduction in body weight gain by Day 9, which may be considered an indication of non-specific maternal toxicity. No effect on Day 11 or Day 20 on embryo-fetal survival, or development was observed.

22-MAR-2001

(26)

Remark: A gavage study compared well-nourished and malnourished in rats given 2.5 g/kg methanol from day 6-15 of gestation. An increase in skeletal malformation, primarily cervical extra ribs was noted in the methanol treated rats when compared to controls. Malnutrition did not increase the incidence of malformations, but fetal growth was retarded. This is only a single dose study and the 2.5 g/kg/day dose is above the lethal dose in humans.

22-MAR-2001
(27)

Remark: Pregnant rats received a drinking solution containing 2% methanol during gestational days 15 through 17 or during days 17 through 19. The average methanol consumption was 2.5 g/kg/day. Behavioral effects such as increased latency to suckling behavior, and a lower efficiency in seeking and reaching their home area were reported. Methanol treatments did not affect the dam (duration of gestation, weight gain or maternal behavior on the day of parturition) or fetus (litter size, birthweight, weight gain, infant mortality or day of eye opening). The behavioral effects noted in this study occur at tissue levels of methanol lower than those associated with teratogenesis in the study by Nelson et al (1985), and may be of potential significance. However, a maternal exposure in this study was 2.5 g/kg/day, which is above the lethal dose in humans.

23-MAR-2001
(42)

Remark: No significant changes in neurobehavioral and neurophysiological development in the offspring of rats exposed to 15,000 ppm methanol vapors (7 hours daily between gestational days 7 and 19) were noted in this study.

23-MAR-2001
(79)

Remark: In an inhalation study in rats exposed to 4,500 ppm for 6 hours per day for day 6 of gestation through day 21 postnatal subtle behavioral changes were reported in both dams and neonates.

23-MAR-2001
(80)

Remark: In a study that evaluated the critical periods for the developmental toxicity of methanol, pregnant CD-1 mice were exposed to 10,000 ppm methanol or filtered air for 7 hr/day on 2 consecutive days during gestation day 6-13, or to single day (7 hr) exposures to 10,000 ppm methanol during gestation day 5-9. Peak maternal blood methanol concentration (at the end of exposure) was ~4 mg/ml, and methanol was cleared from maternal blood within 24 hr. Some fully resorbed litters

were observed with 2-day methanol exposures on gestation day 6-7 or 7-8, or 1-day exposure on gestation day 7. With 1-day methanol exposure on gestation day 7, the number of live fetuses was lower than with exposure on any other day. Cleft palate, exencephaly, and skeletal defects were the fetal anomalies observed. These results indicate that gestation and early organogenesis represent a period of increased embryonal sensitivity to methanol in mice.

23-MAR-2001
(65)

Remark:

Cephalic neural tube defects were observed in near-term mouse fetuses following maternal inhalation of methanol at a 15,000 ppm for 6 hr/day on gestation day 17. Neural tube defects, chiefly exencephaly, occurred in 15% of fetuses (reduction or absence of multiple bones in the craniofacial skeleton, prematurely open eyelids, cataracts, and retinal folds). Following daily 6-hour maternal inhalation of 15,000 ppm methanol during gestation day 7-8, the cephalic neural fold margins were swollen, blunted, and poorly elevated on gestation day 8.5 and 9 relative to controls. Histopathology of exposed gestation day 8.5 embryos revealed microcephaly, reduced mitotic index in the embryonic neuroepithelium and groups of neural crest cells were displaced to the neural folds dorsal to the foregut. When examined on gestation day 9.5 and 10.5, maternal methanol exposure (15,000 ppm for 6 hr/day) during gestation day 7-9 resulted in stunting, delayed rotation, and microcepholy in over 90% of the affected embryos. Many 10.5-day-old embryos were edematous. Occult neural tube defects was present in at least 21 % of methanol-exposed embryos on gestation day 9.5 and 10.5. There were no apparent neural tube defects in control embryos at any stage of development. These data suggest 1) that exposure to high concentrations of methanol injures multiple stem cell populations in the neurulating mouse embryo and 2) that significant neural pathology may remain in older conceptuses even in the absence of gross lesions.

23-MAR-2001
(14)

Remark:

Female mice were given 2.5-g/kg methanol by gavage for twice daily, gestation day 6-10 plus 400 or 1200 nmol folic acid for 5 weeks prior to mating through gestation. The marginal folic acid dietary treatment (400 nmol) resulted in low maternal liver, red cell and low fetal tissue folic acid concentrations. Marginal folic acid-methanol treatment resulted in an increase in the litters affected by cleft palate and exencephaly. These results show that marginal folate deficiency in pregnant dams significantly increases the teratogenicity of methanol.

23-MAR-2001
(35)

Remark:

Female mice were fed one of three diets containing 400 (low), 600 (marginal, or 1,200 (adequate) nmol folic acid diet for 5 weeks prior to and following mating. On gestation days 6-15,

dams received distilled water or methanol at 2.0 or 2.5 g/kg body weight, twice daily. Maternal liver folate concentrations were lower in the low dietary folic acid groups than in the marginal and adequate groups; methanol did not affect maternal liver folate concentration at term. Maternal net gestational weight gain was lowest at the lowest dietary folate level but was not affected by methanol. Gravid uterus weights were lowest in the low dietary folic acid groups exposed to the high methanol dose and the number of live fetuses per litter was lowest in the low folic acid groups. Fetal body weights were lowest in the low folic acid groups and significantly lower in the methanol groups relative to vehicle treated animals. Fetal crown-rump lengths were shorter in the methanol-treated groups; this parameter was not affected by folic acid treatment. Both methanol and low dietary folic acid increased the incidence of cleft palate, with the highest number of affected litters in the low dietary folic acid group. These results support the concept that maternal folate status can modulate the developmental toxicity of methanol.

23-MAR-2001
(69)

Remark: Pregnant mice were gavaged with 0, 4.0, or 5.0 g/kg methanol split in two doses on gestation day 7, the most sensitive day for induction of skeletal alterations by methanol. These results demonstrate that maternal methanol exposure can alter segment patterning in the developing mouse embryo, producing posteriorization of cervical vertebrae

23-MAR-2001
(22)

Remark: In a pilot study methanol given (0.5, 1.0 or 2.0 %) in the drinking water on gestation day 6-15 induced developmental effects in folate deficient Long-Evans rats. Skeletal effects were seen at the top two doses

23-MAR-2001
(68)

DISCUSSION OF SPECIES DIFFERENCES

The toxicity of methanol varies greatly between different species, depending on the ability to metabolize formate. In such cases of slow metabolism of formate, fatal methanol poisoning occurs as a result of metabolic acidosis and neuronal toxicity, whereas, in animals that readily metabolize formate, CNS depression (coma, respiratory failure, etc.) is usually seen. Sensitive primate species (humans and monkeys) develop increased blood formate concentrations following high level methanol exposure, while resistant rodents, rabbits and dogs do not.

Humans (and non-human primates) are uniquely sensitive to methanol poisoning and the toxic effects in these species is characterized by formic metabolic acidosis, ocular toxicity, nervous system depression, blindness, coma and death. Nearly all of the available information on methanol toxicity in humans relates to the consequences of acute rather than chronic exposures.

A vast majority of poisonings involving methanol has occurred from drinking adulterated beverages and from methanol-containing products. Although ingestion dominates as the most frequent route of poisoning, inhalation of high concentrations of methanol vapor and percutaneous absorption of methanol could produce acute toxic effects.

An experimental study of dermal exposure with neat methanol in human volunteers for the purposes of estimating percutaneous absorption rates was conducted. A large percentage (mean of 68%) of the dermally-applied methanol evaporated within 60 minutes (Raabe et al., 1992). The maximum concentration of methanol in blood following an exposure to one hand lasting -20 min is comparable to that reached following inhalation exposures at a methanol concentration of 200 ppm, the threshold limit value-time weight average (TLV-TWA) (Batterman and Franzblau 1997).

The lethal dose of methanol for humans is not known for certain. The minimal lethal dose of methanol in the absence of medical treatment is estimated to be around 1 g/kg. The minimum dose causing permanent visual defects is also unknown. Two important constituents of human response to methanol appear to be (1) concurrent ingestion of ethanol, which slows the entrance of methanol into the metabolic pathway, and (2) hepatic folate status, which governs the rate of formate detoxification.

The symptom and signs of methanol poisoning in humans, usually will not appear until about 12 to 24 hours after exposure, and include visual disturbances, nausea, abdominal and muscle pain, dizziness, weakness and disturbances of consciousness ranging from coma to clonic seizures. Visual disturbances generally develop between 12 and 48 h after methanol ingestion and range from mild photophobia and misty or blurred vision to markedly reduced visual acuity and complete blindness. In extreme cases death can result. The principal clinical feature is severe metabolic acidosis largely attributed to the formic acid produced when methanol is metabolized.

The normal blood concentration of methanol in humans from endogenous sources is less than 0.5 mg/liter (0.02 mmol/liter), but dietary sources may increase blood methanol level. Generally, transient Central Nervous System (CNS) effects appear above blood methanol levels of 200 mg/liter (6 mmol/liter); ocular symptoms appear above 500 mg/liter (16 mmol/liter) and fatalities have occurred in untreated patients with initial methanol levels in the range of 1500-2000 mg/liter (47-62 mmol/liter). Metabolic acidosis and ocular toxicity characterize methanol toxicity in humans and monkeys, and appears to be due to the accumulation of formate. This accumulation is due to a deficiency in formate metabolism, which results from low hepatic tetrahydrofolate (H4 folate) levels. Humans and monkeys possess low hepatic H4 folate levels. This results in low rates of formate oxidation and accumulation of formate after large doses of methanol (Tephly-1991).

Acute inhalation of methanol vapor concentrations below 260 mg/m³ or ingestion of up to 600 mg methanol by healthy or moderately folate-deficient humans does not result in formate accumulation above endogenous levels (Lee et al 1992, Leon et al., 1989).

Ocular toxicity, a well-recognized outcome of methanol poisoning in humans, correlates with formate accumulation in blood. Total folate levels were determined in human and rat retinal tissues and were found to be much lower than the levels in liver. However, folate levels in human retina were only 14%

of those determined in rat retina. The amount of 10- formyl tetrahydrofolate dehydrogenase (10-FDH) in human retina was approximately three times the amount found in rat retina. 10-FDH was found to be preferentially localized in the Mueller cells, which appear to represent the target for formate induced ocular toxicity. Formate oxidation reactions might serve two roles, first a protective role and then a role in methanol-induced toxicity in Mueller cells (Martinasevic et al., 1996).

Role of metabolism on the species differences

Animal tests were done over the years to obtain predictive information. The investigation of methanol toxicity in animals is somewhat difficult to correlate to human effect because normal rodents exposed to methanol do not display the metabolic acidosis and toxicity to the visual system that occurs in humans (Roe 1982, Tephly and McMartin 1984; World Health Organization 1997).

The monkey is most like man when it comes to formate level following exposure to methanol. Chronic methanol exposures (2.5 hours per day, 0, 200 600 or 1,800 ppm) for up to 1 year in *m. fascicularis* females was studied by Burbacher (1999). The study included measuring blood methanol and plasma formate levels. While blood methanol levels increase with dose, no changes in blood formate levels were noted (Burbacher et al 1999). In a single inhalation exposure of a Rhesus monkey for 6 hours at 2000 ppm resulted in no increase in formate levels (Horton et al., 1992).

NEDO (1987) also exposed rats and primates to methanol by gavage and measured blood formate levels. Only at 3000 mg/kg were formate levels evaluated in both species. Lower doses (25, 125 and 600 mg/kg) showed no elevation in blood formate. This is consistent with a toxic dose (optic injury, minimum lethal dose) in humans of about 1000 mg/kg (Roe 1982).

In a study by Andrews et al (1987) monkeys exposed to 5,000 ppm methanol for 6 hours per day, 5 days/week showed no treatment-related changes when compared to the controls.

NEDO (1987) exposed primates nearly continuously for up to 14 days (20+ hours a day, 7 day per week). In this nearly continuous sub-acute exposure study toxicity was noted at 5,000 ppm but not at 3,000 ppm. The toxicity observed at 5,000 ppm correlates with the increase in formate level observed at 5,000 ppm (but not at 3,000 ppm).

The difference in the response in the two studies is most likely due to the difference in exposure patterns. The NEDO studies used 20+ hours exposure per day. The half-life on methanol in the body is 1-3 hours (Burbacher et al., 1999). The NEDO study design gives a possibility for the build-up of methanol and formate in the body because of lack of clearance time. In the Andrews et al (1987) study exposure was for 6 hours per day with 18 hours for clearance. The difference in the response at 5,000 ppm in the two studies might be explained by the total daily dose between the two studies.

Using Haber's law ($CT=K$) the total dose is much greater in the NEDO studies [NEDO- 3,000 ppm (3,000 x 20 hrs =60,000 ppmhr), 5,000 ppm (5,000 x 20 hrs = 100,000 ppmhr)] versus [Andrews -5,000 ppm (5,000 x 6 hrs = 30,000 ppmhr)]. The results of this comparison suggest that between 60,000 ppmhr and 100,000 ppmhr there is formate build-up in the 14 day NEDO study, but the lack of clearance makes it difficult in the NEDO studies to get an accurate daily dose over time.

Burbacher et al (1999) evaluated the effects of methanol inhalation exposure on pregnant monkeys exposed at a top daily dose of 4500 ppmhr (1800 ppm x 2.5 hrs). The top dose in this study was a NOAEL. The Andrews et al (1987) data suggest the NOAEL could be higher than the top dose used by Burbacher et al (1999).

Incorporation of kinetic parameters and the fraction of inhaled methanol absorbed in humans and rodents into kinetic models indicate that an 8-hour exposure to 5,000 ppm methanol produced some very different results in different species.

The blood methanol level in the mouse is 13-18 times higher and in the rat it is 5 times higher than in humans exposed to the same 5,000 ppm inhaled level (Perkin et al., 1995). This species difference may also be related to the difference in response of pregnant animals to methanol. The mouse is the most sensitive showing developmental effects below a maternal toxic doses while the rat only responds at higher doses that are maternally toxic.

There is abundant data on the potential health effects of methanol in humans. Most information on the human health effects of methanol is derived from clinical observations following accidental or intentional ingestion of methanol. Methanol can be highly toxic, resulting in nausea, dizziness, metabolic acidosis, and toxicity to the visual system (including blindness), motor disturbances and even death in humans. Exposure of humans to 200 ppm does not increase blood formate levels or result in any toxicity (Lee et al., 1992).

The absorption of methanol is rapid following oral ingestion, inhalation of methanol vapor, or skin contact. High doses of methanol overwhelm the humans body's ability to remove a toxic metabolite (formate). When formate accumulates, toxicity occurs.

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